THE COMPLEX JOURNEY OF A VACCINE – PART II
Immunization supply chain, delivery innovation, and regulatory requirements
THE IMMUNIZATION SUPPLY CHAIN COMPLEXITY

EXECUTIVE SUMMARY

Research to foster new innovation and improvements to existing vaccines continues despite the significant investment required, the uncertainty of use by public sector purchasers, and the unpredictability of forecasted demand.

The optimization of supply chain is extremely important to reduce the cold chain footprint, limit wastage rates, and increase vaccination coverage, compliance, and safety.

With a line-of-sight focused on enabling expanded access of vaccines to resource-poor settings, vaccine manufacturers are investigating the heat-stability targets of current vaccines and as a criterion in their upstream developments, optimizing packaging and labeling, and developing novel delivery devices.

However, the benefits from these advancements will not be fully realized unless there is also progress in the areas of regulatory convergence and harmonization, facilitated approvals, country-level infrastructure upgrading, sustainable supply chain training, and demand forecasting.

No single country, organization, company, or community can meet vaccines delivery challenges alone. Cooperation and coordination are important elements to ensure an effective and rapid response to achieve the above changes.

IFPMA vaccine manufacturers encourage immunization partners to consider the potential long-term impacts of today’s programmatic policies and standards to address in-country downstream logistical complexities on ongoing investment in R&D, manufacturing capacity, and future vaccine supply.

IFPMA supports the WHO’s Global Vaccine Action Plan calling for a shift in approach that will improve the immunization supply chain around the world, to increase access to, and use of, effective vaccines, from a public health, development, and universal health coverage perspective.
Continuous improvement of the vaccine delivery process is important to ensure that the right vaccine is in the right place, at the right time, and under the right conditions. Although UNICEF and other global partners may be responsible for delivery at the national level, improving vaccine delivery from shipment through administration is a shared concern requiring close collaboration amongst all stakeholders.

Vaccine manufacturers are thus committed to help realize the goals of accelerated vaccine delivery, and equitable vaccine uptake and coverage as stated in the Decade of Vaccine (DOV) Global Vaccine Action Plan (GVAP). Yet, this cannot happen without a strong Immunization Supply Chain and Logistics (ICSL) systems in place.

This sequel to the “Complex Journey of Vaccine” published in 2014 depicts the delivery part of vaccines. This edition examines in details the delivery needs, particularly adapted to remote settings. It also offers some of the solutions that manufacturers are working on to improve vaccine delivery to low-resource settings and highlights the associated regulatory challenges.

What makes vaccine supply delivery chain so complex?

How can vaccine delivery innovations be deployed expeditiously and not be subjected to protracted delays due to diverse and localized regulatory requirements?

1  WHO Immunization Supply Chain and Logistics http://goo.gl/DLZZWX
2  WHO Decade of Vaccines Global Vaccine Action Plan 2011-2020, Table 7, Page 70 http://tinyurl.com/oubpszz
VACCINE SUPPLY CHAIN COMPLEXITY

The role of the supply chain is to ensure effective vaccine storage, handling, and stock management; rigorous temperature control in the cold chain; and maintenance of adequate logistics management information systems. The ultimate goal is to ensure the uninterrupted availability of quality vaccines from manufacturer to service-delivery levels, so that opportunities to vaccinate are not missed because vaccines are unavailable. To ensure an uninterrupted supply of quality vaccines to patients, the regulatory environment needs to reflect the complexity of new vaccines and Good Manufacturing Practices (GMP).

- Vaccines are complex biological products that often require “cold chain” storage, i.e. temperature control of 2 to 8°C.
- As the Expanded Programme on Immunization (EPI) has been extended to include new vaccines and the number of doses of vaccine required increased, there is mounting pressure to increase performance of national immunization supply chain and logistics systems.
- Adequate supply chain management is critical: failure to store and handle vaccines properly can diminish vaccine effectiveness, consequently leading to inadequate immune responses in patients and poor protection against diseases. The public’s trust in vaccination may be eroded if the vaccines people receive have been compromised (for example, exposed to inappropriate conditions/temperatures or simply mishandled).

The Difference between Vaccines and Small Molecules

Vaccine Components:
- large and complex molecular assemblies
- active components taken from living microorganisms
- highly susceptible to environmental factors (e.g. temperature) that may significantly affect their activity

Small Molecule Components:
- relatively simple structures
- derived from chemical compounds
- generally more stable to environmental factors

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4 World Health Organization (WHO) Immunization supply chain and logistics (ISCL) http://www.who.int/immunization/programmes_systems/supply_chain/en/
6 Conference report “From refrigerator to arm: Issues in vaccination delivery”; LJTan; Vaccine 32 (2014) 2389-2393
7 http://www.who.int/biologicals/vaccines/Annex_3_WHO_TRS_962-3.pdf?ua=1
8 http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3564302/
New immunization landscape (1980-2013)" 

- Provide protection against 2.5 times as many diseases, e.g. overview of Gavi, the Vaccine Alliance – global vaccine access initiative.\(^9\)
  - 2014 Japanese encephalitis
  - 2014 Cholera
  - 2013 IPV
  - 2013 Measles rubella
  - 2013 HPV
  - 2011 Meningitis A
  - 2009 Pneumococcal
  - 2008 Rotavirus
  - 2007 Measles
  - 2006 Pentavalent
  - 2002 Hib
  - 2001 Yellow fever
  - 2001 Hepatitis B

- Immunize populations across the lifespan – from infants to adults.

- Administer 3 times as many doses per child.

- Store and transport 4 times more vaccine volume per fully immunized child.

- Serve a global target population that has doubled in size.

Immunization Supply Chain & Logistics (ISCL) systems challenges

- Inventory unpredictability
- Inadequate cold chain capacity
- Insufficient funding

ISCL systems are struggling, and often failing, to cope with these increased demands – resulting in stock-outs, potential administration of ineffective vaccines (e.g. when potency is lost due to inadequate management), avoidable wastage, and inadequate cold chain capacity.

A recent study of 57 Gavi-eligible countries\(^11\) concluded that less than 25% of countries are operating at the minimum Effective Vaccine Management (EVM) levels for maintenance, stock management, and distribution and that only 30% of countries are meeting minimum standards for temperature control.

Recent findings from Pakistan show a loss of USD 3.7 million in wastage of donated vaccines due to poor storage.\(^12\)

Vaccine Incident Report from WHO Vigibase, by error type, December 2012

<table>
<thead>
<tr>
<th>Error Type</th>
<th>Incidents</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incorrect vaccine administered</td>
<td>4,238</td>
<td>21.6</td>
</tr>
<tr>
<td>Administration error</td>
<td>336</td>
<td>1.7</td>
</tr>
<tr>
<td>Incorrect dose administered</td>
<td>1,473</td>
<td>7.5</td>
</tr>
<tr>
<td>Accidental overdose</td>
<td>484</td>
<td>2.5</td>
</tr>
<tr>
<td>Incorrect form</td>
<td>184</td>
<td>0.9</td>
</tr>
<tr>
<td>Expired vaccine</td>
<td>50</td>
<td>0.2</td>
</tr>
<tr>
<td>Other vaccine incident types</td>
<td>14,321</td>
<td>73.0</td>
</tr>
<tr>
<td>Total vaccine incidents</td>
<td>19,613</td>
<td>100%</td>
</tr>
</tbody>
</table>

9 WHO Immunization Supply Chain and Logistics http://www.who.int/immunization/call-to-action_ipac-iscl.pdf
10 Comparing the requirements of Immunization Supply Chain & Logistics (ISCL) systems in the 1980’s to the present (Source: http://www.who.int/immunization/sage/meetings/2013/november/1_ISCL_Key_Challenges.pdf)
Supply chain experts from the public and private sectors agree that “In an environment with limited resources, protecting every child with lifesaving vaccines may not be possible without also improving the design and presentation of vaccines themselves (…) many supply chain problems can be best addressed at the earlier stages of vaccine development where decisions relating to formulation, packaging, labelling, and presentation can make vaccines more suitable for distribution, storage, and use in low-resource environments.”

The research-based vaccine manufacturers are working with the public sector to formulate, package, and label vaccines to optimize the usage of existing cold chain capacity, address transportation space concerns, reduce wastage, and secure preparation and administration, particularly in resource-limited settings.

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How do we facilitate the movement?

How do we prevent missed opportunities?

How do we develop the capacity of the frontline worker?

District Cold Store Facilities

Clinics Static Outreach

Regional District Subdistrict Community Village

Frontline Workers Issues

Cold Chain Breaks

Logistics & Transportation Constraints
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SUPPLY CHAIN DELIVERY

INTERNATIONAL SHIPPING AND VACCINE ARRIVAL

- Space and weight of packages
- Cold chain
- Environmental sustainability
- Quantity and quality control check at reception
- Time out of refrigeration

CHALLENGES

- Packaging optimization
- E-labeling

DISTRICT/REGIONAL STORE

- Storage
- Electricity supply
- Stock management & forecast
- Transportation
- Temperature excursion management
- Shipping solutions, cost, and efficiency

EXAMPLES OF INNOVATION

- Real time data support over the entire shelf life. New formulations to withstand heat. New refrigeration techniques
  - Solar powered refrigerator
  - Resistant cold boxes

Temperature control: 2°C / 8°C

Disposal / waste management

Manufacturing
+
- 24 months

Vaccine ready to be shipped

HEALTH CENTER

- Last mile logistics
- Cold chain

Temperature monitoring technologies
- Vaccine Vial Monitor (VVM)
- Peak temperature threshold indicator for CTC

VACCINE PREPARATION

- Complex preparation for vaccine use
- Counterfeit

Improved and harmonized labeling
- E-labeling
- Barcode

Simpler presentations
- Liquid, instead of freeze-dried, form

VACCINE ADMINISTRATION AND SCHEDULE COMPLIANCE

- Patient adherence
- Documentation (Inventory and patients’ records)
- Risk of misuse leading to safety risk and vaccine failure for the patient
- Risk of needle stick injuries for the healthcare worker

Auto-disable features (no reuse)
- Needle free injection
- Uniject
- Jet injector
- E-labeling
- Barcode

Lack of trained staff

Safe preparation and administration
Research-based vaccine manufacturers are testing the temperature stability of current vaccines for after several days without refrigeration, in addition to long-term storage at recommended temperature conditions. In the longer term, manufacturers are applying similar tests to new technologies and formulations for vaccines in development.

A controlled-temperature chain is defined as the storage and transport temperatures above the traditional 2-8°C, which may allow product exposure to 40°C for 4 days, before administration, under monitored and controlled conditions, and as appropriate to the stability of the antigen.16,17

What value CTC brings?
- Expand immunization coverage in settings where maintaining the cold chain is not feasible – for example, during the transportation of vaccines from health centres during outreach vaccination campaigns.
- Easier outreach of vaccination campaigns by facilitating local logistics and transportation.
- Lower cost associated with vaccination. Fewer freezers, fewer journeys and less staff time are needed to manage and maintain cold chain requirements.19
- Reduce vaccine wastage as a result of accidental freezing of vaccines from cold packs, since many vaccines cannot bear freezing temperatures.

However, it is important to note that some vaccines are intrinsically unstable when exposed to high temperatures even for short periods of time. Hence, the CTC approach may not work for all vaccines.

Vaccines Cold Chain
Vaccines are kept between 2-8°C (36-46°F). This cold chain requires intense logistics in resource-limited settings.

Challenges when Traveling the Last Mile:
- Lack of large transportation vehicles
- Limited refrigeration

For example: Vaccines against cholera, hepatitis B, human papillomavirus (HPV), malaria, and pneumococcal diseases will be soon available for use in CTC.18

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16 WHO Controlled Temperature Chain (CTC). http://www.who.int/biologicals/areas/vaccines/controlledtemperaturechain/en/
17 For further information, please also refer to the WHO Film on the Controlled Temperature Chain (CTC) http://www.who.int/immunization/programmes_systems/supply_chain/resources/tools/en/index6.html and https://www.youtube.com/playlist?list=PL9S6xGsoqIBWYg1540xBQ3XFvzzZJRrPt
18 IFPMA Vaccines Travelling the Last Mile http://www.ifpma.org/uploads/media/IFPMA_Report_Vaccines_Traveling_the_Last_Mile.pdf
What is meant by presentation?

The pharmaceutical presentation of vaccines refers to the combination of the type of primary packaging (i.e. single-dose vial, multi-dose vial, ampoule, pre-filled syringe) and the type of secondary packaging (i.e. single dose vial assembled by 100 in a carton box).

Manufacturers are addressing packaging size concerns, while remaining mindful of the diverse needs of frontline health care workers for vaccination campaigns. Among other things, manufacturers are converting, when possible, pre-filled syringes, which occupy more volume per dose to single dose vials, reducing and harmonizing the size of primary, secondary, and tertiary containers, as well as developing multi-dose vial presentations and combination vaccines. The aim is to make choices available that are easy to transport and administer.

What is meant by packaging?

The first level of packaging refers to the vial, ampoule, prefilled syringe, or other container that is in direct contact with the vaccine.

The second level of packaging is what holds the primary container(s) (e.g., cartons containing one or more vials or prefilled syringes of vaccines) and the package insert.

The third level of packaging is the outer box or the shipping box containing multiple secondary packaging.20

EXAMPLE 2: PACKAGING AND PRESENTATION OPTIMIZATION

In CTC, no ice packs are required.

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20 Adapted from http://www.gov.mb.ca/health/publichealth/cdc/coldchain/protocol7.html
Pfizer changed the pneumococcal vaccine presentation from a prefilled glass syringe to a single-dose vial for use in the developing countries. The change in packaging and presentation reduced the cold chain space per dose required from 55.9 cm$^3$ to 12 cm$^3$.

Crucell (Part of the Janssen Pharmaceutical Companies of Johnson & Johnson) reduced the packaging size of pentavalent vaccine from 13 to 10 cm$^3$ per dose, allowing an increase of the vial capacity of the tertiary packaging of 17%.

GSK’s (GlaxoSmithKline) first-generation rotavirus vaccine was lyophilized (freeze-dried) and required to be reconstituted with a supplied diluent. This needed a significant amount of cold storage space. GSK addressed this by changing the lyophilized presentation requiring 156 cm$^3$ per dose to a ready-to-use liquid presentation in an oral applicator requiring 85.3 cm$^3$ per dose. GSK then developed a plastic tube presentation requiring only 17.1 cm$^3$ of space per dose to store and transport.
These examples illustrate that presentation and packaging optimization can deliver significant benefits in the optimal utilization of existing cold-chain storage in low-resource settings with limited cold-chain supply infrastructure.

Developing new vaccine presentations can provide advantages such as reduce the cold chain footprint, limit wastage rates, and increase vaccination coverage, compliance and safety.

Manufacturers are also exploring the development of digital solutions, such as e-labeling to provide clear and legible product and storage information that will improve people’s safety. E-labeling could be particularly helpful as product package size is being reduced to optimize the cold-chain footprint.

2D DataMatrix barcoding of vaccines is being explored by our public health partners to optimize vaccine supply chain and stock management in low and middle income countries. Vaccine manufacturers are working collaboratively with a Gavi-funded PATH demonstration project team consisting of vaccine manufacturers, UNICEF, WHO, GS1, and the Tanzania Expanded Programme on Immunization team to demonstrate the technical, user, economic, and regulatory aspects of capturing vaccine product information using 2D bar technology.

By integrating the technical, practical, and user requirements, this demonstration project aims to show how to build an appropriate system to capture and use bar code data located on vaccine packaging to support vaccine management and supply chain decisions.

21 Image courtesy of Jeong-Woo Lee, Laboratory for Drug Delivery, Georgia Institute of Technology in http://www.pnas.org/content/110/25/10049/F1.expansion.html
23 http://www.3rdstonedesign.com/project/real-mccoy/
3 COMPLEX REGULATORY REQUIREMENTS

Undertaking innovations to overcome supply chain challenges, such as changing the packaging, presentation, and CTC, requires considerable investments in the manufacturing operations and regulatory tasks by vaccines manufacturers. Our goal is to make choices available that are easy to transport and administer so that we never miss an opportunity to vaccinate.

Overall, any modification after a vaccine has been approved by regulatory authorities must be reviewed by each national regulatory authority before the new vaccine can be distributed in the country, with significant differences in approval times worldwide24. Differences in approval times can have serious consequences on vaccine access and security of supply. Due to limited production capacities, manufacturers cannot always simultaneously maintain different lines of production for the multiple approved versions of the vaccine.

Furthermore, new delivery devices require additional clinical trials to demonstrate that they are equivalent or better in terms of safety and efficacy than the original delivery device. Changes to a vaccine’s presentation may require additional approvals by national regulatory agencies that have responsibility for medical devices.

Similarly, once the necessary validation of the CTC has been confirmed (including stability studies and potentially clinical data), the vaccines manufacturers would need to obtain national regulatory approval of the necessary CTC label changes before implementation.

Unfortunately, these regulatory processes may differ in timelines and requirements among countries, creating a large amount of complexity for global vaccine suppliers.

Promote convergence and harmonization of regulatory standards to enable timely vaccine approval, access, and security of supply.

Collaborate with well-resourced and expert regulatory authorities to leverage their experience.

Use the WHO Prequalification process to accelerate the local regulatory review and approval, in countries with limited regulatory capabilities.

Foster dialogue with vaccine manufacturers to align on the development of guidelines on optimal vaccine CTC usage, storage and handling, presentations, and packaging.

Ensure awareness that CTC does not apply to all vaccines and must be validated before implementation.

Support the training of healthcare providers on appropriate usage of vaccines with new presentation and CTC label.

We welcome the opportunity to continue working with partners to remove any barriers to vaccinating children, adolescents, and adults.

**Disclaimer**

This graph is intended to help the reader understand the impact of delayed regulatory approvals upon supply and access to vaccines. It is fictionalised, based upon industry experience of managing complex regulatory variations but it does not represent an actual example. Regulatory lead-times are variable and can be influenced by many factors such as medical need.
ABOUT THE IFPMA
IFPMA represents the research-based pharmaceutical companies and associations across the globe. The research-based pharmaceutical industry’s 2 million employees research, develop and provide medicines and vaccines that improve the life of patients worldwide. Based in Geneva, IFPMA has official relations with the United Nations and contributes industry expertise to help the global health community find solutions that improve global health.
www.ifpma.org

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